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Analysis of the Role of Indicator Technics In Quantitation of Valvular Regurgitation

By Homer R. Warner, M.D., Ph.D.

■ Although the usefulness of certain indicator methods in the evaluation of patients with valvular regurgitation is now well established, many of the technics currently in use do not yield consistently accurate information. Since these failures may be due to lack of an adequate theoretical basis for interpretation of the indicator-dilution data obtained, further exploration into the logical foundation upon which these technics rest seems worth while. In this paper a mathematical model (fig. 1) of the left side of the heart is presented and used as a basis for predicting the time course of indicator concentration to be logically anticipated in the left atrium, left ventricle, and aorta following injection into each of these chambers or into a pulmonary artery in the presence or absence of mitral or aortic valvular regurgitation.

Mathematical Representation of Left Side of Heart

First I shall describe with a set of ordinary differential equations the time course of blood flow, volume and pressure in the chambers of the left side of the heart. The rate at which the volume (V_1) of the left atrium changes with time is the sum of the flow into the atrium from the pulmonary veins (Q_1) and from the left ventricle (Q_3) minus the flow out of the atrium into the ventricle (Q_2) and is given by

$$\frac{dV_1}{dt} = Q_1 + Q_3 - Q_2. \qquad (1)$$

Q_1 varies with the respiratory cycle but is independent of the cardiac cycle. This is expressed in

$$Q_1 = A + B \sin(\omega t + \Phi) \qquad (2)$$

where A is the mean Q_1, B is a parameter that defines the maximal change in Q_1 from the mean at any phase of the respiratory cycle, ω is the frequency of the respiratory variations in intrathoracic pressure, and Φ is the phase angle between the maximal intrathoracic pressure and maximal Q_1. Sinusoidal variations in intrathoracic pressure are assumed for convenience. Q_2 is zero during ventricular systole, and during diastole it is given by

$$a_1 \frac{dQ_2}{dt} + b_1 Q_2 = P_1 - P_2 = K_{1d} V_1 - K_{2d} V_2 \qquad (3)$$

where a_1 is the pressure gradient required to accelerate the flow of blood across the mitral valve at a rate of 1 ml./sec.$^{-2}$, b_1 is the resistance to flow across the mitral valve during diastole, and K_{1d} and K_{2d} represent the ratio during diastole of pressure to volume in the left atrium and left ventricle respectively and are treated as constants in the first approximation. These latter two parameters might, of course, be treated as functions of time or volume. Q_3 is zero during diastole, and during systole it is given by

$$a_2 \frac{dQ_3}{dt} + b_2 Q_3 = P_2 - P_1 = K_{2s} V_2 - K_{1s} V_1 \qquad (4)$$

where a_2 and b_2 are the inertiance and resistance to flow across the mitral valve during systole and K_{1s} and K_{2s} represent the ratio of pressure to volume for the left atrium and left ventricle during systole. The rate of change of volume of the left ventricle (V_2) is given by

$$\frac{dV_2}{dt} = Q_2 - Q_3 - Q_4 + Q_5 \qquad (5)$$

where Q_4 and Q_5 represent flow across the aortic valve in systole and diastole respectively and are given by

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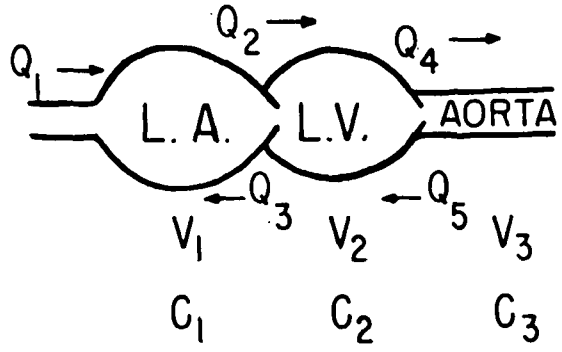

FIGURE 1

Diagram of model of left side of heart. Terms are defined in the text.

$$a_3 \frac{dQ_4}{dt} + b_3Q_4 = P_2 - P_3 = K_{2s}V_2 - K_3V_3 \quad (6)$$

and

$$a_4 \frac{dQ_5}{dt} + b_4Q_5 = P_3 - P_2 = K_3V_3 - K_{2d}V_2 \quad (7)$$

where b_3 and b_4 are the resistance to flow across the aortic valve in systole and diastole and K_3 is the ratio of pressure to volume in the aorta. Q_4 is zero during diastole and Q_5 is zero during systole. The rate at which the volume of the aorta (V_3) changes with time is given by

$$\frac{dV_3}{dt} = Q_4 - Q_5 - \frac{K_3}{b_5} V_3 \quad (8)$$

where b_5 is the resistance to forward flow out of the aorta (peripheral resistance). These eight differential equations must be solved simultaneously in order to express the course of each of these variables as a function of time for any given set of system parameters. One analog-computer solution to these equations is shown in figure 2. Here is shown the predicted time course of flow and volume in the absence of valvular regurgitation. These wave forms represent flow from left ventricle to aorta (Q_4) (which is zero during diastole), flow from left atrium to left ventricle (Q_2) (which is zero during systole), and volume of left atrium (V_1), left ventricle (V_2) and aorta (V_3) as a function of time. In figure 3 is shown the time course of flow and volume when "mitral and aortic regurgitation" is present. Q_3 is backflow across the mitral valve and Q_5 across the aortic valve. The effect of changing any one parameter on the time course of each of these variables may be readily studied in such a model by simply adjusting the appropriate potentiometer.

Now in order to define the expected time course of concentration of an indicator in the left atrium (C_1), left ventricle (C_2) and aorta (C_3) following injection into any of these chambers, it is only necessary to define the nature of the mixing process. Although, in reality, mixing is undoubtedly not instantaneous throughout the left atrium or ventricle,[1, 2] such an assumption is made here in order to examine the logical consequences to which this assumption leads. Also it is assumed that the concentration of indicator at the root of the aorta equals the left ventricular concentration during systole and remains constant during the succeeding diastole, that is, blood in the ascending aorta is completely replaced by new blood ejected with each systole.

The mass of indicator in the atrium (M_1) and ventricle (M_2) is obtained by integration of

$$\frac{dM_1}{dt} = Q_1C_0 - Q_2C_1 + Q_3C_2 \quad (9)$$

and

$$\frac{dM_2}{dt} = Q_2C_1 - (Q_3 + Q_4)\, C_2 + Q_5C_3 \quad (10)$$

where C_0 is the concentration of dye in pulmonary-vein blood entering the left atrium. A term, $\dot{n}t_i$, must be added to equation 9 in the case of left atrial injection, or to equation 10 in the case of left ventricular injection. $\dot{n}$ is the rate of injection of indicator and t_i is the duration of injection. The concentration terms follow from the definitions

$$C_1 = \frac{M_1}{V_1} \quad (11)$$

and

$$C_2 = \frac{M_2}{V_2} \quad (12)$$

and must be generated after the integration

of equations 9 and 10 since V_1 and V_2 are variables. As already stated, C_3 equals C_2 during systole and remains constant during the succeeding diastole.

To solve these equations on an analog computer, relays are used to set the boundary conditions for systole and diastole as prescribed by the equations.[3] These relays are controlled with a timing circuit set to correspond to the duration of systole and diastole that normally occurs at the particular heart rate being studied.

These equations will now be used to explore the logical conclusions to which the assumptions lead in the analysis of certain indicator technics that are currently employed for the quantitative assessment of mitral and aortic valvular regurgitation. First to be considered is the injection of indicator into the left ventricle with detection of concentration in the left atrium (C_1) and the left ventricle (C_2) for the quantitative estimation of flow from ventricle to atrium in mitral regurgitation.

The curves shown in figure 4 represent a solution of equations 1 through 12 for the variables C_1 and C_2 resulting from a simulated injection of indicator into the left ventricle during diastole. It can be seen that C_2 decreases with each diastole and remains constant during systole, while C_1, the indicator concentration in the left atrium, increases with systole and decreases during diastole. Lacy and associates[4] have suggested the use of

$$\frac{\bar{Q}_3}{\bar{Q}_2} = \frac{\Sigma\ \bar{C}_{1d}}{\Sigma\ \bar{C}_{2s}} \qquad (13)$$

for estimation of the ratio of average backflow ($\bar{Q}_3$) from ventricle to atrium over a whole cycle to average forward flow ($\bar{Q}_2$) from atrium to ventricle over the whole cycle where $\bar{C}_{1d}$ is the average concentration of indicator in the atrium during each ventricular diastole and $\bar{C}_{2s}$ is the average concentration of indicator in the left ventricle during each systole. Each of these concentrations is summed for the number of heart cycles necessary to clear the indicator from

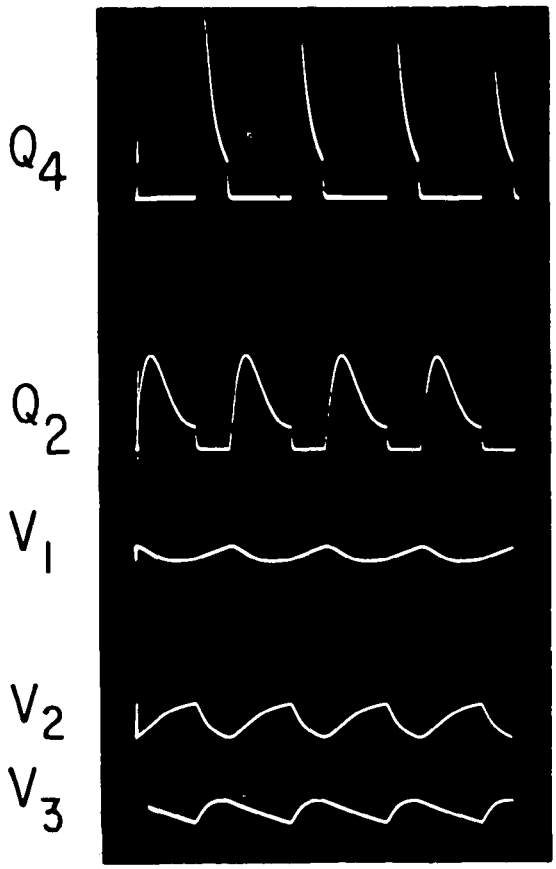

FIGURE 2

Simultaneous solution of flow and volume equations 1 through 8 obtained with an analog computer. Q_3 and Q_5 are set to zero.

atrium and ventricle. In fact, however, equation 13 is not true in the general case unless either Q_3 or C_2 is constant during the course of systole and either C_1 or Q_2 is constant during diastole. It can be seen that C_2 is constant during each systole, but neither C_1 nor Q_2 is constant in diastole.

Recently, Sinclair and associates[2] have used a modified form of this approach to assess experimentally produced mitral regurgitation in dogs. These authors measured the ratio of the area under a left atrial dye curve to the area under a dye curve obtained from a femoral artery following injection into the left ventricle. They found that the prediction of regurgitant flow using this ratio correlated ($r = 0.96$) with regurgitant flow

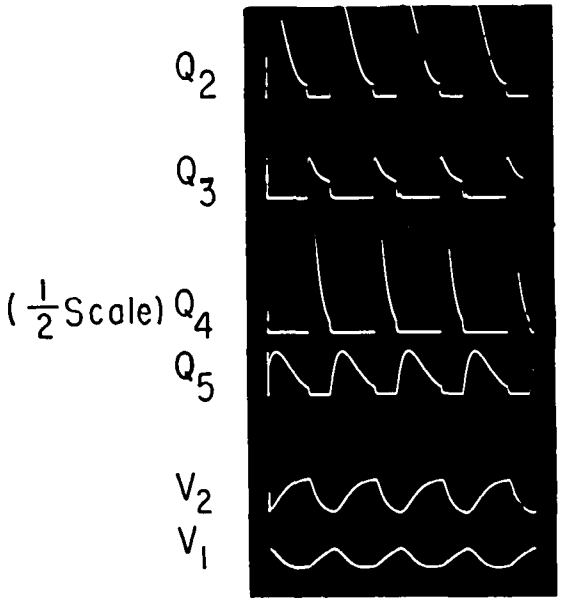

FIGURE 3

Solution of flow and volume equations in the presence of mitral regurgitation and aortic regurgitation. The resistance to regurgitant flow across the mitral valve is equal to 40 times the resistance to forward flow in this instance. Resistance to backflow across the aortic valve is equal to 1.4 times resistance to forward flow across the aortic valve.

estimated by the hydraulic formula of Gorlin and Dexter[5] using the pressure gradient measured during the experiment and the cross-sectional area of the defect as measured at necropsy.

From the theoretically derived curves shown in figure 4, prediction of the ratio of Q_3 to Q_2 underestimates the actual ratio by 5.4 per cent when the ratio of the total area under the two dilution curves is used. That the error involved in using this approximation is small may result from the fact that the systolic and diastolic time course of variation in C_1 are fairly symmetrical.

It is of special interest in regard to the practical application of this technic that Sinclair and co-workers found that the estimated regurgitant fraction in a given dog was not dependent upon the site of injection in the left ventricle and was dependent upon the site of sampling in the left atrium only when the sampling catheter was actually in a pulmonary vein or in the cephalad region of the atrium. Consistent ratios were obtained in the midatrium and near the mitral valve.

Next to be considered is the possibility of measuring Q_3 from an indicator-dilution curve recorded downstream from the injection. In figure 5 is shown the time course of dye concentration in the left ventricle following injection into the left ventricle with and without mitral regurgitation. The curve labeled "normal" was obtained with Q_3 set to zero and the curve labeled "M.I." was obtained with Q_3 equal to 0.64 times the net cardiac output. It can be seen that the down slope of the curve is very insensitive to the presence of Q_3. In figure 6, end-systolic residual volume of the ventricle was varied from 50 to 100 ml. and produced a marked change in the shape of the curve. The time constant of the down slope increased to 1.5 times its original value when end-systolic residual left ventricular volume was increased from one half to two thirds of the end-diastolic ventricular volume as shown at the bottom of this figure.

From these two results it is obvious that even in the ideal case, in which injection is made in a single diastole into the left ventricle and mixing is complete, the use of the down slope for measurement of Q_3 would be unsatisfactory. In figure 7 is shown the time course of C_1 and C_3 when the concentration of dye entering the left atrium from the pulmonary veins (C_0) has the time course shown here, as it might have following an injection into the pulmonary artery. In such a case, it is not possible to measure Q_3 from the aortic curve as Korner and Shillingford[6] attempted to do, since no independent measurement of the effect of left atrial and left ventricular volume can be made. In the case of left ventricular injection and left ventricular or aortic sampling it would theoretically be possible to determine Q_3 since left ventricular end-diastolic volume may be measured from the concentration of indicator in the ventricle during the first systole following a diastolic injec-

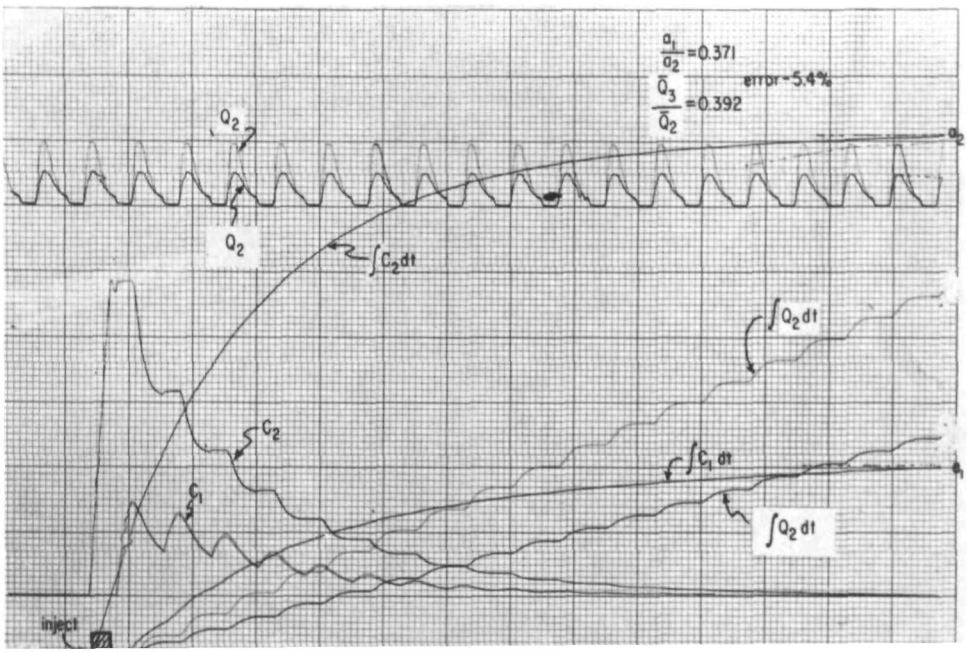

FIGURE 4

At the top is shown the time course of Q_2 with and without mitral regurgitation. Below is shown the time course of C_2 and C_1 following injection of indicator into the left ventricle during diastole. These two indicator-concentration curves are integrated and the ratio of the integrals is compared to the ratio of Q_3 to Q_2 as used by Sinclair and co-workers.[2] $\bar{Q}_3$ is the difference between values for $\bar{Q}_2$ with and without mitral insufficiency.

tion. This has independently been pointed out by Polissar and Rapaport.[7]

However, in spite of these theoretical objections, it must be said that downstream indicator-dilution curves have proved of value in providing semiquantitative, if indirect, information regarding the presence and severity of clinical mitral regurgitation. An example of such an index is shown in figure 8. Here is plotted the reciprocal of the time constant (τ) of the exponential down slope of the indicator-concentration curve against the build-up time (t_b) of the curve. It can be seen that there is a fair separation of the patients with mitral regurgitation from the patients without mitral regurgitation, but there are certain exceptions as has been found with other such empiric indices. Unfortunately, the exceptions are often the very cases in which the diagnosis of mitral regurgitation may be uncertain on other grounds as well. This index is based on the observation that mitral regurgitation prolongs the descending limb of the curve more than the ascending limb. Such selective prolongation might occur if a relatively abrupt unsmeared curve were to enter a large left atrium or left ventricle. An extreme example of this is the case of injection of all the indicator into the left ventricle in a single diastole as illustrated in figure 4. In this case the peak concentration is reached in the first heart cycle. In the case of injection into the left atrium the result is much the same, namely the build-up time of the aortic curve depends upon the time-course of indicator concentration in blood entering the atrium while the down slope may be prolonged by a large left atrium or left ventricle. The ability of this index to detect mitral regurgitation must depend, then, upon the occurrence in

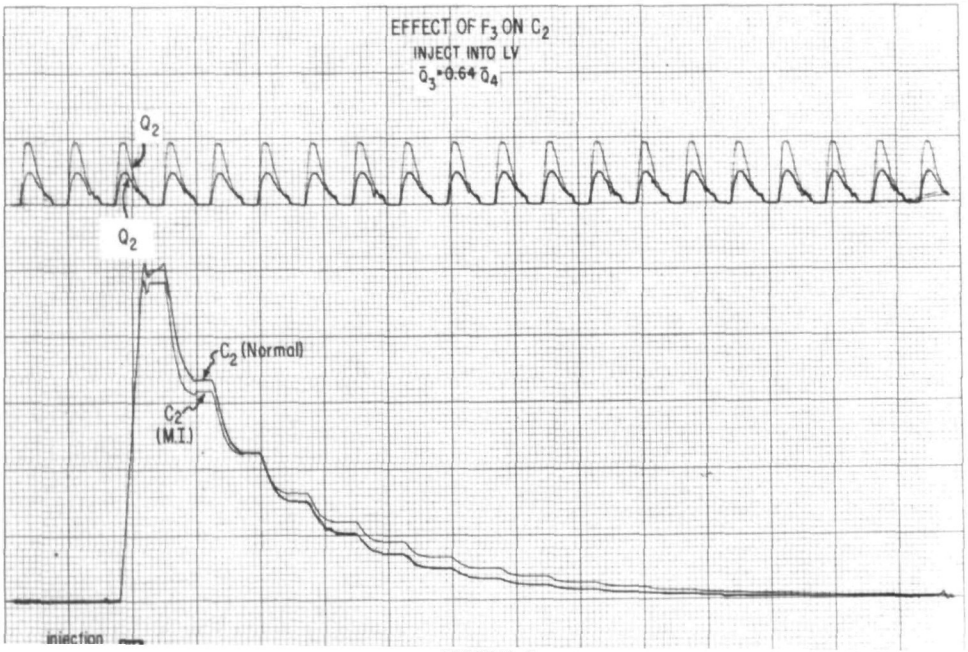

FIGURE 5

Comparison of the time course of C_2 with and without mitral regurgitation in the presence of a constant mean left ventricular and left atrial volume. The time course of Q_2 with and without mitral regurgitation is shown at the top.

mitral regurgitation of left atrial or left ventricular enlargement, or both, out of proportion to the changes in the pulmonary circulation which "smear" the dilution curve by the time it enters the left atrium, or upon the occurrence of a peculiar mixing of indicator in the left atrium or left ventricle in mitral regurgitation. Militating against the latter argument is the observation that acute mitral regurgitation in dogs does not produce the typical distortion of an indicator-dilution curve seen in patients with long-standing mitral regurgitation.

Other indices have been proposed whose ability to separate patients with mitral regurgitation from patients with other cardiac defects is dependent upon the relationship of the amount of "smearing" of the dye curve as it passes through the pulmonary circulation and left side of the heart to the "smearing" that occurs as the indicator passes around the whole circulation or the right side of the heart and the systemic veins. One example of this is the C_L/C_R ratio proposed by Wood and Woodward.[8] C_L is defined as the minimal concentration of dye obtained during the descending limb of the curve before recirculation again increases the concentration, and C_R is the peak concentration achieved during the recirculation hump of the curve. C_L is dependent only on events taking place as the indicator goes from the pulmonary artery to the sampling site in a systemic artery, and C_R will be influenced by events occurring in the whole circulation. Perhaps the fact that this index is relatively successful in separating patients with mitral regurgitation from those without regurgitation is the result of a selective dilatation of the left ventricle, left atrium, and, possibly, pulmonary vascular bed as compared to the systemic veins and right side of the heart in patients with mitral regurgitation.

Lange and Hecht[9] have injected dye into a peripheral vein and recorded simultaneously the concentration of dye in the pulmonary artery and a systemic artery. The

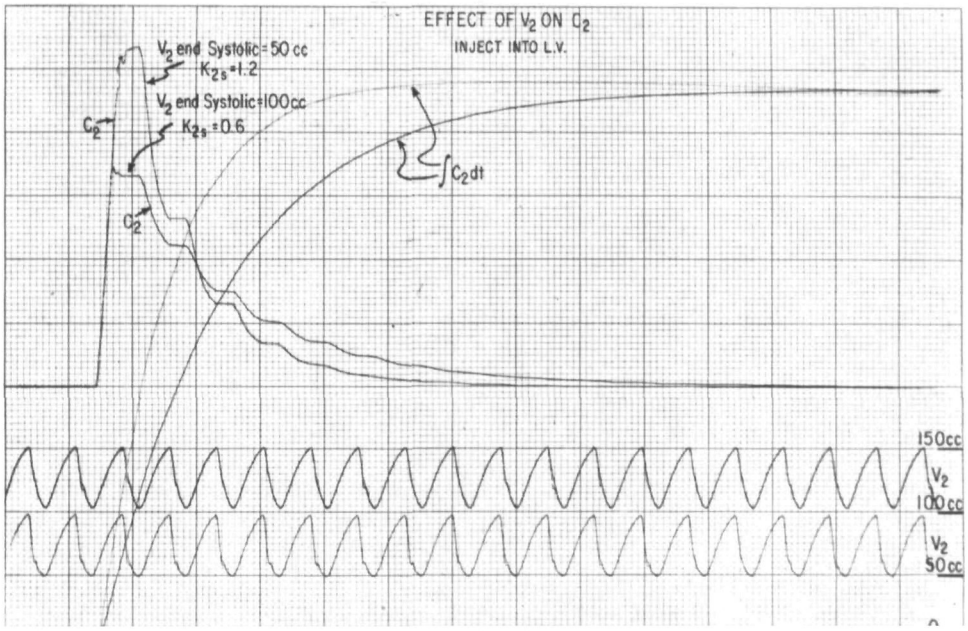

FIGURE 6

Effect of increasing end-systolic residual volume of the left ventricle on the time course of C_2 following left ventricular injection.

difference in appearance time and mean circulation time between the two curves is used to estimate the severity of mitral regurgitation. This approach to the detection of mitral regurgitation once again depends upon the relative "smearing" of indicator with passage through the pulmonary circulation and left side of the heart as compared to the effects of passage of indicator from a systemic vein to the pulmonary artery. Since this "smearing" is largely determined by the volume of the left atrium and left ventricle and not by the magnitude of regurgitant flow (Q_3), this index, like the others just presented, cannot be expected to yield direct information regarding Q_3.[10]

It is apparent that more theoretical and experimental work must be done to clearly define all the factors responsible for the observed alteration in contour of a dilution curve that results from its passage through the various component parts of the circulation. From such information and a better understanding of the pathologic physiology of mitral regurgitation, the use of indicator technics for quantitation of mitral regurgitation may attain the accuracy and reliability required for the solution of the practical problems which face the clinician.

Aortic Regurgitation Methods

First to be considered is the possibility of measuring regurgitant flow across an aortic valve from a downstream curve following injection into the left ventricle. If the injection is made in diastole and mixing is complete in the left ventricle, the concentration of dye during the first systole, both in the left ventricle and in the aorta, will be equal to the amount of indicator injected divided by the end-diastolic value of V_2. This volume is the sum of the residual end-systolic volume of the left ventricle, the net stroke volume entering from the left atrium, and the regurgitant stroke volume entering from the aorta. During the next diastole, blood that enters the left ventricle from the aorta will have the same concentration of indicator as the blood remaining in the ventricle from the previous systole and will have the same effect on the subsequent

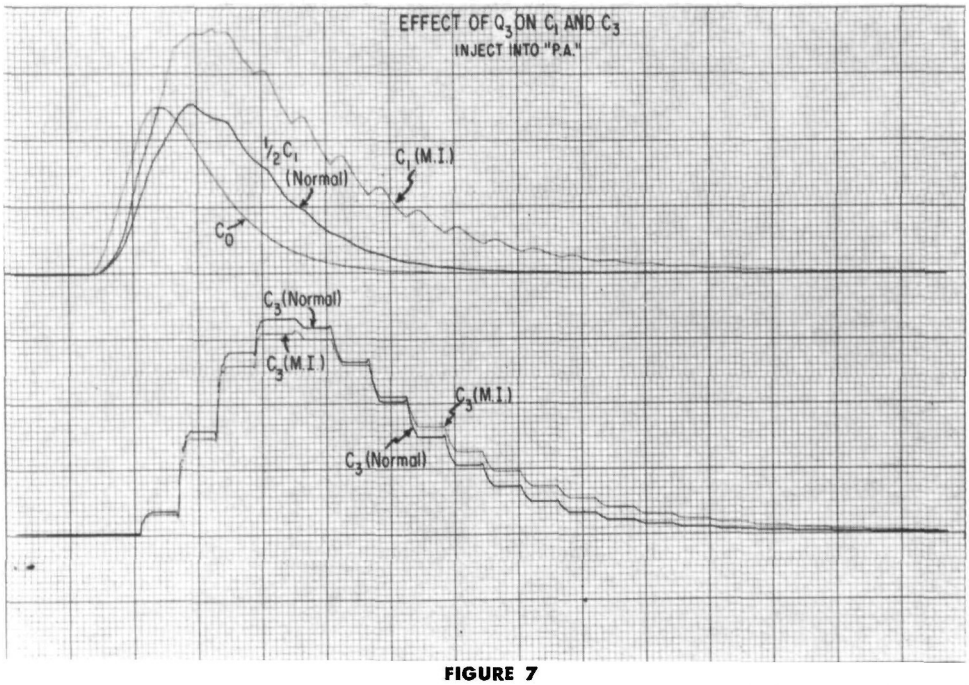

FIGURE 7

Predicted time course of C_3 with and without mitral regurgitation following a simulated injection into the pulmonary artery. C_0 is the wave form chosen to represent the time course of dye concentration in blood entering the left atrium from the pulmonary veins. The scale factor on this curve is arbitrary.

end-diastolic left ventricular concentration of dye as would have occurred had the residual left ventricular volume been increased by an amount equal to the regurgitant stroke volume. Thus, the downstream dye curve in aortic regurgitation cannot permit the quantitation of regurgitant flow across the aortic valve unless an independent measure of the end-systolic residual volume is available. Unfortunately, this information cannot be obtained by means of the indicator-dilution principle, since the very presence of aortic regurgitation invalidates the premises upon which this technic depends.

Injection of indicator into the aorta and simultaneous measurement of its concentration in the left ventricle and in a peripheral artery have been used by Armelin and coworkers[11] to estimate the backflow across the aortic valve in aortic regurgitation from

$$\frac{\bar{Q}_5}{\bar{Q}_4} = \frac{a_1}{a_2} = \text{regurgitant fraction} \quad (14)$$

where $\bar{Q}_5$ is the mean flow over the whole heart cycle from aorta to left ventricle, $\bar{Q}_4$ is the mean flow from left ventricle to aorta over the whole heart cycle, a_1 is the area under the indicator-concentration curve recorded from the left ventricle, and a_2 is the area under the indicator-concentration curve recorded from a femoral artery. Since equation 14 is based upon the same principle as equation 13 for flow across the mitral valve, it is essential that the fraction of injected indicator that regurgitates into the left ventricle be representative of the fraction of the total forward flow of blood that regurgitates. To analyze this, the results of an injection timed with respect to the heart cycle will be considered. If the injection occurs early in diastole and is short (0.1 second), all of the dye might be carried back into the left ventricle, resulting in a regurgitant fraction of one, even if the severity of aortic regurgitation is minimal.

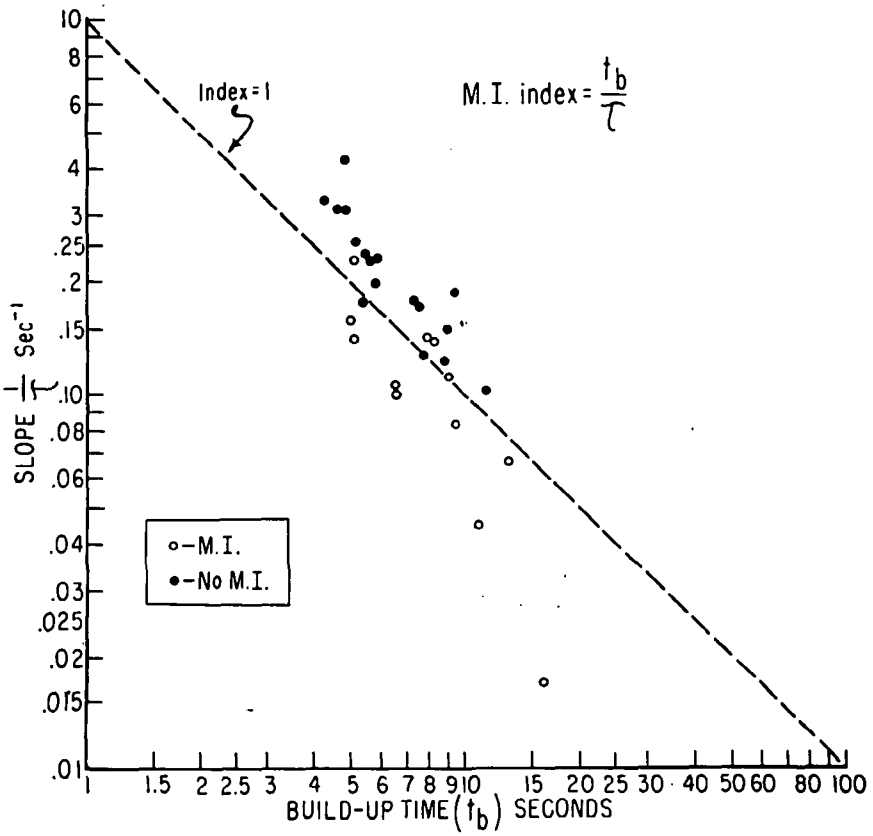

FIGURE 8

Comparison of the down slope ($1/\tau$) of the exponential descending limb of a femoral-artery dilution curve following pulmonary-artery injection of indicator to the build-up time (t_b) in patients with and without mitral regurgitation as proved at operation. Broken line indicates an index of one.

All that is required for this to occur is that the labeled blood in the first few centimeters of the aorta be replaced during diastole with unlabeled blood from farther down the aorta. Even if the injection were carried over the whole heart cycle, that fraction injected during diastole would be subject to the error just described. On the other hand, if the injection were carried out just over the duration of systole, an overestimate of backflow might still be expected since the concentration of dye expressed at the end of systole as a function of distance down the aorta from the aortic valve would not be uniform, but would depend upon the time course of flow velocity during systole past the injection site. The highest concentration of dye would be closest to the aortic valve, since flow velocity out of the ventricle is maximal early in systole. This may explain why Armelin and associates found no significant difference between the estimates of regurgitation with this technic made from dye injections carried out over the duration of systole, over the duration of diastole, and over the whole cycle, since by this technic an overestimate of regurgitant flow would be expected in all three cases.

Another method for estimation of backflow in aortic regurgitation involves the injection of indicator into the descending aorta and detection of indicator concentration in blood from the left radial artery[12] (or use of an oximeter at the right ear[13]). Repeated

injections of indicator are made into the aorta, each time at a distance 2 cm. farther from the origin of the subclavian artery until a point is reached at which injection no longer results in appearance of indicator at the left radial sampling site on the first circulation. The distance from the origin of the left subclavian artery to this point is taken as the distance over which backflow in the aorta travels during a single diastole. This distance multipled by the cross-sectional area of the aorta would represent the volume of blood regurgitating from this segment of the vascular bed in one diastole. This estimate would be valid if the farthest-traveling particles of indicator were representative of the whole column of blood as is the case with the "bubble flowmeter." However, Warner and Toronto[14] have recently shown that increasing the heart rate results in a much more drastic decrease in aortic regurgitation estimated by this technic than could be explained by taking into account the change in the fraction of the heart cycle occupied by diastole at the increased rate and by reasonable assumptions regarding the inertia of the blood column. They concluded that the progressive development of laminar flow during diastole caused an apparent marked increase in aortic insufficiency at slow heart rates. Thus, in using this technic as a practical semiquantitative index of aortic regurgitation, heart rate at the time of the study must be taken into consideration.

Conclusions

From the analysis here presented, the following conclusions regarding the use of indicators for the quantitative evaluation of mitral and aortic regurgitation may be drawn:

1. Even with the assumption of complete mixing in the left atrium and left ventricle, large fluctuations in the time course of indicator concentration in the left atrium may be expected following sudden single injection of indicator into the left ventricle in the presence of mitral regurgitation. Despite these pulsatile variations in the time course of left atrial concentration of indicator and the simultaneous variation in the time course of flow across the mitral valve in diastole, it should be possible to estimate the magnitude of the mitral regurgitant flow within about 5 per cent by using the modification of equation 13 employed by Sinclair and associates.[2] Whether this accuracy is possible with less complete mixing cannot be answered.

2. From the analysis based on this mathematical model of a pulsatile heart with complete mixing assumed in the left atrium and left ventricle, it has been demonstrated that detection and quantitation of mitral regurgitation from an indicator-dilution curve recorded from the left ventricle following injection of indicator into the left ventricle is possible but difficult since the shape of the curve is quite insensitive to regurgitant flow, compared to its sensitivity to changes in volume of the left atrium and left ventricle. Moreover, direct quantitation of mitral regurgitation is impossible following injection into the pulmonary artery or left atrium, since other much more critical determinants of the curve, namely left atrial and left ventricular volume, cannot be measured from such a curve.

3. Quantitation of aortic regurgitation from an indicator-concentration curve recorded downstream from the left ventricle is not possible because the effect of the regurgitant stroke volume is indistinguishable from the effect of increasing the end-systolic residual left ventricular volume by an identical amount. Furthermore, the determination of left ventricular end-systolic volume by means of an indicator-dilution technic is not possible in the presence of aortic regurgitation.

4. Both the detection of indicator in the left ventricle following aortic injection and the determination of maximal backflow distance that indicator particles travel up the aorta during a single diastole tend to overestimate the severity of aortic regurgitation. The extent of the overestimate is directly

related to the duration of diastole, at least with the latter technic.

Some theoretical objections have been raised (in this paper) to the quantitative interpretation of information derived from the use of indicator technics for the evaluation of valvular regurgitation. It seems reasonable to expect, however, that further analysis of the factors measured by the various indices of valvular regurgitation currently in use may increase the usefulness of these technics as tools for the practical evaluation of patients suspected of having valvular regurgitation.

References

1. IRISAWA, H., WILSON, M. F., AND RUSHMER, R. F.: Left ventricle as a mixing chamber. Circulation Res. 8: 183, 1960.
2. SINCLAIR, J. D., NEWCOMBE, C. P., DONALD, D. E., AND WOOD, E. H.: Experimental analysis of atrial sampling technic for quantitating mitral regurgitation. Proc. Staff Meet., Mayo Clin. 35: 700, 1960.
3. WARNER, H. R.: The use of an analog computer for analysis of control mechanisms in the circulation. Proc. IRE 47: 1913, 1959.
4. LACY, W. W., GOODSON, W. H., WHEELER, W. G., AND NEWMAN, E. V.: Theoretical and practical requirements for the valid measurement of indicator-dilution of regurgitant flow across incompetent valves. Circulation Res. 7: 454, 1959.
5. GORLIN, R., AND DEXTER, L.: Hydraulic formula for calculation of the cross-sectional area of the mitral valve during regurgitation. Am. Heart J. 43: 188, 1952.
6. KORNER, P. I., AND SHILLINGFORD, J. P.: Further observations on the estimation of valvular incompetence from indicator dilution curves. Clin. Sc. 15: 417, 1956.
7. POLISSAR, M. J., AND RAPAPORT, E.: A mathematical pulsatile model of the human heart: Application to analysis of indicator curves. Presented at postdoctorate summer course, International School of Physics, Varenna, Italy, July, 1960.
8. WOOD, E. H., AND WOODWARD, E., JR.: A simple method for differentiating mitral regurgitation from mitral stenosis by means of indicator-dilution curves. *Proc. Staff Meet., Mayo Clin.* 32: 536, 1958.
9. LANGE, R. L., AND HECHT, H. H.: Quantitation of valvular regurgitation from multiple indicator-dilution curves. Circulation 18: 623, 1958.
10. MARSHALL, H. W., WOODWARD, E., JR., AND WOOD, E. H.: Hemodynamic methods for differentiation of mitral stenosis and regurgitation. Am. J. Cardiol. 2: 24, 1958.
11. ARMELIN, E., MICHAELS, L., MARSHALL, H. W., DONALD, D. E., AND WOOD, E. H.: Detection of retrograde passage of indicator from aorta to left ventricle in dogs. (Abstr.) The Physiologist 3: 10 (Aug.) 1960.
12. WARNER, H. R., AND TORONTO, A. F.: Quantitation of backflow in patients with aortic insufficiency using an indicator technic. Circulation Res. 6: 29, 1958.
13. BRAUNWALD, E., AND MORROW, A. E.: A method for the detection and estimation of aortic regurgitant flow in man. Circulation 17: 505, 1958.
14. WARNER, H. R., AND TORONTO, A. F.: Effect of heart rate on aortic insufficiency as measured by a dye-dilution technique. Circulation Res. 9: 413, 1961.